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Treatment of Dentin Hypersensitivity Using Nano-Hydroxyapatite Pastes: A Randomized Three-Month Clinical Trial

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Clinical Relevance

New bioactive agents seem to have a promising effect in reducing hypersensitivity discomfort.

SUMMARY

Objectives: This randomized clinical trial tested the three-month desensitizing effect of two protocols using nano-hydroxyapatite formulations compared with Pro-Argin and fluoride varnish.

Methods: Twenty-eight subjects with 137 teeth presenting dentin exposure with a minimal hypersensitivity of four on the visual analog scale (VAS) took part of this study. The subjects were randomly assigned to four groups: Desensibilize Nano-P paste (20% hydroxyapatite [HAP], potassium nitrate, and sodium

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fluoride [NaF]; 9000 ppm fluoride [F]); Desensibilize Nano-P associated with experimental home-care pastes (10% HA, potassium nitrate, and NaF; 900 ppm F); Pro-Relief professional paste (8% arginine with Pro-Argin technology) associated with home-care toothpaste (8% arginine, sodium monofluorophosphate, 1450 ppm F); and Duraphat professional varnish (NaF varnish, 22,600 ppm F). The professional treatments were performed in weekly appointments over three weeks. The home-care products were used continuously for three months. A VAS was used to assess the tooth sensitivity response after standardized evaporative stimulus at baseline and after one month and three months. The baseline score was deducted from the final score, and the means were analyzed using nested analysis of variance, while the comparison between times was performed by a general linear model ($p<0.05$).

Results: At the first month all treatments were effective, but there were no significant differences among them ($p=0.94$). At the third month, despite the fact that NaF varnish had the lowest effect in reducing hypersensitivity, no significant difference was found among the treatments ($p=0.09$). Only Pro-Relief increased its effect over time ($p=0.049$).

Conclusions: Nano-hydroxyapatite formulations (with or without home-care product association) were as effective as the other treatments in reducing dentin hypersensitivity over three months.

INTRODUCTION

Dentin hypersensitivity (DH) is a painful clinical condition that has a negative effect on quality of life and often affects adults worldwide.[1-6] The condition results from dentin exposure mainly resulting from gingival recession or continuous loss of dental structure promoted by erosion, abrasion, and/or abfraction.[5-7] The DH mechanism is still uncertain, and the most acceptable hypothesis is based on the hydrodynamic theory.[8] Thus, most treatment options focus on controlling dentin fluid movement.[3,9] Accordingly, therapeutic agents that promote the occlusion of the dentin tubule apertures, such as fluoride-based agents, are interesting strategies.[10,11]

Among such agents, sodium fluoride (NaF) varnish has been one of the most commonly indicated in the treatment of DH.[9,11-16] The mechanism of action of highly concentrated fluoride (F) products is attributed to the precipitation of calcium fluoride (CaF_2) on the dental surface, which forms a mechanical barrier that obliterates tubule apertures,[12] potentially minimizing DH.[9,13,15] Even if the effect of NaF varnish on DH relief is assumed to be limited[11,13] and descending after three and six months of application,[14] Kielbassa and others[16] found a relief effect after three weeks, which was stable for 12 months after application of a lacquer containing NaF/CaF_2.

Recently, other agents using different ingredients, such as oxalate and strontium salts, bioglasses, and arginine/calcium carbonate, have been developed in the search for a long-lasting effect.[5,17] Pro-Argin (8.0% arginine), an in-office desensitizing paste available on the market, provided hypersensitivity relief compared with a negative control.[18] However, no data are available comparing the Pro-Argin professional paste with other therapies for DH. Pro-Argin is also available as home-care toothpaste that can be indicated in association with the in-office treatment.[19] According to Cummins and others,[20] this product physically seals dentin tubules by forming plugs containing arginine, calcium carbonate, and phosphate, which are said to be resistant to normal pulpal pressures and acid challenges. Therefore, it effectively reduces dentin fluid flow and thereby relieves sensitivity instantly and lastingly.[5,20]

Another potential element used to treat DH is nano-hydroxyapatite (nano-HA), which is considered one of the most biocompatible and bioactive materials and is widely applied in medicine and dentistry as a bone substitute and for tooth remineralization.[21,22] Evidence has demonstrated that nano-sized particles have similar morphology, structure, and crystallinity compared with dental apatite.[23] Recent reports have shown that nano-HA has good potential for remineralizing enamel carious lesions,[24-26] but limited information is available with respect to the treatment of DH.[27] Therefore, comparative clinical trials including other popular desensitizing methods need to be carried out to prove its effect.

The aim of this clinical trial was to compare the effect of nano-HA pastes indicated for professional (Desensibilize Nano-P) with or without experimental home-care application to Pro-Argin (new technology), and fluoride varnish (already established treatment) on DH relief after one and three months of treatment. The tested null hypotheses were that 1) there are no significant differences between nano-HA pastes and the other desensitizing protocols, regardless of the time of analysis, and 2) there is no

significant difference between both times of analysis for each tested desensitizing protocol.

METHODS AND MATERIALS

Experimental Design

The research was planned as an interventional, randomized, prospective, single-center, double-blind (subjects and the researcher LW), parallel, and four-cell clinical trial. This study was registered with UTN 1111-1134-6945 (http://www.ensaiosclinicos.gov.br/) and followed the CONSORT guideline.

Subjects Selection and Ethical Aspects

Subjects who presented for DH treatment at the Bauru School of Dentistry were considered in this trial. Twenty-eight patients (7 men and 21 women, aged between 18 and 60 years old) with 137 hypersensitive teeth were enrolled in this study according to eligibility criteria. The inclusion criteria required at least one tooth with DH higher than four on a visual analog scale (VAS), while the exclusion criteria eliminated subjects with active carious lesions or defective restoration on the selected tooth; dentin loss that needed restorative treatment or periodontal surgery; any professional desensitizing treatment in the previous six months or use of desensitizing toothpaste in the previous three months; using analgesics/anti-inflammatory drugs at the time of study; pregnancy, or smoking.

The research was ethically conducted in accordance with the Declaration of Helsinki. Ethical approval for the study involving human subjects was granted by the local Ethics Committee (#160/2010). Informed consent was obtained from all subjects prior to the study. The subjects received written instructions and a schedule and were extensively trained for all procedures.

Six weeks before and during the study (three months), the subjects received oral hygiene instructions for brushing their teeth three times a day (after two main meals and before sleeping), using a soft toothbrush (Oral B, Rio de Janeiro, Brazil), fluoride toothpaste (Condor, São Bento do Sul, Brazil, except the subjects from the Pro-Relief group, who used Pro-Relief toothpaste instead of Condor), and dental floss (Sanifill, São Paulo, Brazil) provided by the researchers. The researchers advised the subjects to make a circular movement on the labial surface of the teeth and to not apply force during brushing.

To ensure that the subjects were blinded about the treatment, the pastes were displayed in the same type of tubes. Subjects were asked to refrain the use of any other product for oral hygiene during the experiment.

Treatments and Sample Size

The subjects were randomly assigned to four treatments using Microsoft Excel for Mac 2011, Version 14.3.5 (Microsoft, Chicago, IL, USA), in which the mean baseline VAS score of all selected teeth per subject was calculated. Based on the initial average VAS score per subject (7.04 ± 1.62), they were randomly assigned to each treatment, ensuring similar mean baseline VAS scores among the treatments. Subjects were distributed in each appointment in a way to also guarantee the blindness of the evaluator. The number of teeth presenting DH was highly distinguished among the selected patients as well as the baseline score and the response of each tooth to the treatment. Therefore, we found it more appropriate to consider the teeth as statistical numbers instead of patient as done in other studies.[13, 28]

A difference of three units between the baseline and final VAS score was considered clinically relevant according to a previous study.[10] A minimal number of 16 teeth per group was needed to get a sample power of 80%. Considering a possible dropout of 25%, we included between six and eight patients per group, with a minimum total of 22 teeth in per group.

Teeth were treated with one of the following materials: nano-HA professional paste containing 20% hydroxyapatite [HAP] in a 100-nm size with potassium nitrate, NaF, and 9000 ppm F (Desensibilize Nano-P, FGM-Dentscare, Joinville, Brazil); nano-HA (Desensibilize Nano-P) and experimental home-care paste containing 10% HA in a 100-nm size with potassium nitrate, NaF, and 900 ppm F (experimental home-care paste; FGM-Dentscare); Pro-argin professional paste containing 8% arginine and calcium carbonate (Pro-Relief Colgate, São Bernardo do Campo, Brazil) and home-care toothpaste containing 8% arginine, calcium carbonate, sodium monofluorophosphate, and 1450 ppm F (Pro-Relief; Colgate); and NaF professional varnish with 22,600 ppm F (Duraphat, Colgate).

The professional treatments were performed for three subsequent weeks, for four minutes each, with an interval of one week between the applications. Three calibrated operators performed the professional applications: After professional cleaning with pumice slurry (Pumice powder extra fine, SSWhite, Rio de Janeiro, Brazil), rinsing, and drying, the

pastes or varnish were applied using microbrushes (KG Brush, KG Sorensen, Cotia, Brazil). The excess was removed after four minutes with a cotton swab, except in the case of the fluoride varnish. The subjects were advised not to drink or eat for 30 minutes after the treatment. In the case of fluoride varnish, the subjects were also asked not to brush their teeth for at least four hours according to manufacturer's instruction.

Over three months, the subjects belonging to the group treated with nano-HA and the experimental home-care treatment were trained to apply the paste twice a day after toothbrushing (the first and last oral hygiene of the day) using a cotton swab on the sensitive teeth for four minutes and then removing the excess. The subjects were again advised not to drink or eat for 30 minutes after the treatment. The subjects from the Pro-Relief group brushed their teeth using Pro-Relief toothpaste instead of the conventional toothpaste that was provided for all other subjects during three months of treatment.

Analysis of the DH

For all appointments, the same researcher conducted the analysis of the DH level. An evaporative stimulus was used to assess the tooth sensitivity response. A strong air-blast from calibrate dental syringe (55-60 psi, 21°C–22°C) was directed perpendicularly to the exposed cervical area no longer than three seconds at a distance of 1 cm, while the other teeth were protected with cotton rolls. The air temperature was measured using a noncontact thermometer (Minitemp FS, IR-thermometer, Raytek, China) in a range of 19°C–23°C. The VAS 10-point scores (from "no pain" to "intolerable" pain) were recorded at baseline and after one month and three months of treatment.

Statistical Analysis

The baseline score was deducted from the final score (at the first and third month separately) for all groups. The difference means were statistically compared using Statistica software version 11 (Statsoft, Tulsa, OK, USA). The assumptions of equality of variances and normal distribution of data were checked for all the variables tested, using the Bartlett and Kolmogorov-Smirnov tests, respectively. As the assumptions were satisfied, a nested analysis of variance design was carried out for the comparison among the treatments (fixed effect) considering tooth as the experimental unit and clustering among teeth within the same subject (random effect). For the comparison between the periods within group, a general linear model with period and subject as random effects was carried out. The significance limit was set at 5%.

RESULTS

A flow diagram of the progress of this randomized clinical trial is presented in Figure 1, highlighting the main phases of the study. At the baseline, first and third months of treatment, the numbers of teeth enrolled in each group were, respectively: Desensibize Nano-P (31, 31, and 30); Desensibize Nano-P and experimental home-care paste (23, 22, and 22); Pro-Relief (33, 28, and 26); and Duraphat professional varnish (50, 50, and 45). The inclusion criteria allowed participants with at least one tooth with DH,[13] but the number of teeth affected by DH in the present study ranged from two to seven per patient. The groups had the following mean number of teeth per subject: Desensibilize Nano-P (4.3 teeth), Desensibilize Nano-P with experimental home-care paste (3.2), Pro-Relief (5.2), and Duraphat (5.5). At the end of the study, 14 teeth were lost due to different reasons: one in the Desensibilize Nano-P group and one in the Desensibilize Nano-P and experimental home-care group (the teeth were restored), seven teeth from the dropout of two subjects in the Pro-Relief group, and five teeth from the dropout of one subject from the fluoride varnish group. The mean baseline VAS scores for all groups were 7.04 ± 1.62.

Table 1 shows the difference between means for the baseline and the final VAS score at the first and third months. All tested treatments were clinically effective in reducing DH, compared with baseline data for each group (>3.0 in VAS difference) except the Duraphat group at the third month. At the first and third months, there were no significant differences among the treatments ($p=0.936$ and $p=0.094$, respectively).

Table 2 presents the comparison between one and three months for each treatment separately. Only Pro-Relief presented significant difference between the periods; its effect was increased at the third month compared with the first month ($p=0.049$).

DISCUSSION

Based on the results, the null hypotheses were accepted (except hypothesis two for Pro-Relief). The present study demonstrated that all treatments had a similar effect on DH, but both the Desensibilize Nano-P and Pro-Relief treatments were effective in producing relevant clinical relief (difference >3.00) for three months.[10] For any treatment, side effects

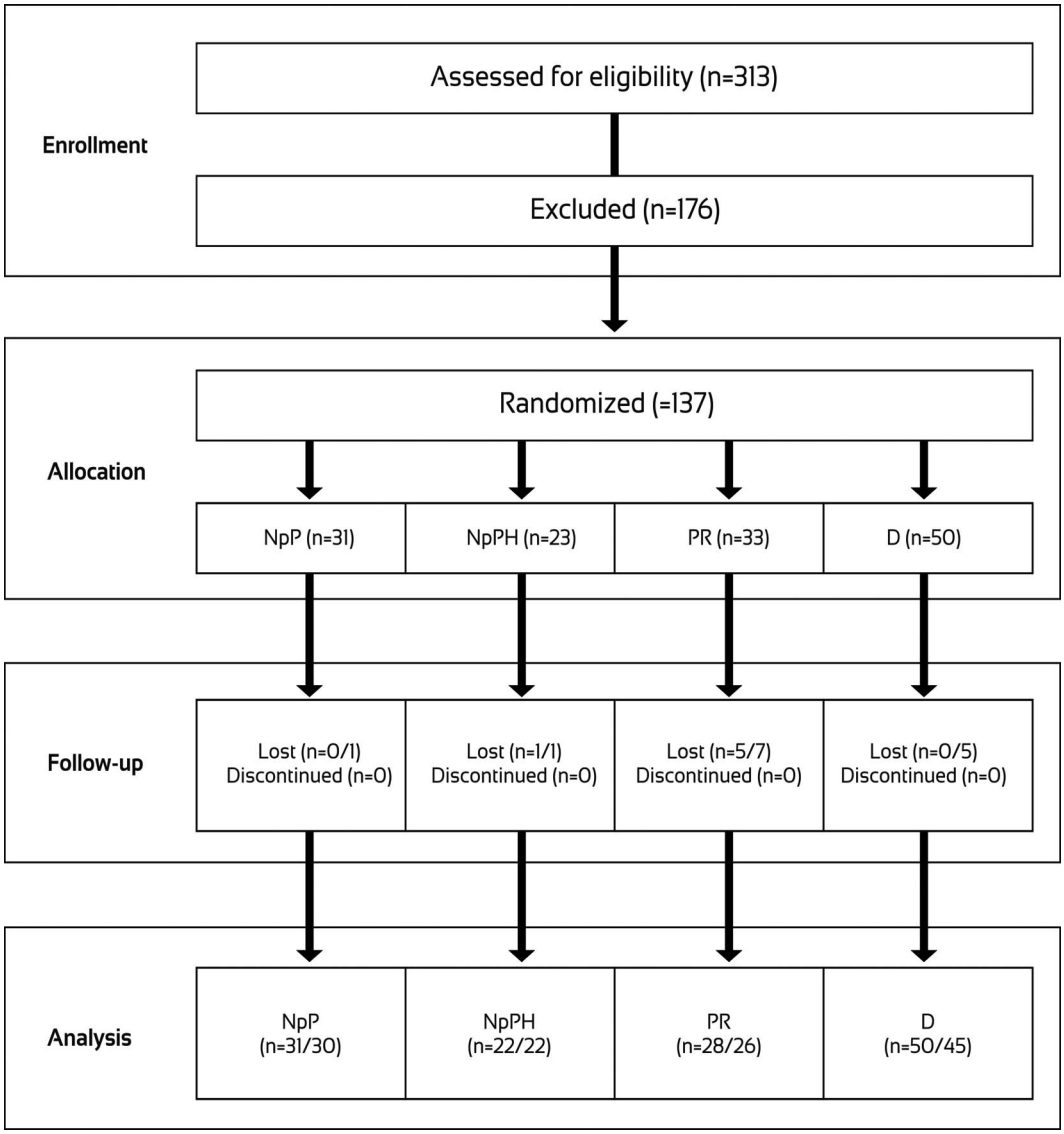

Figure 1. *Flow diagram of the progress through the phases of this randomized trial.*

were not registered. Furthermore, Pro-Relief presented a significant increasing effect through the time, however, there was no difference compared with the other treatments at the third month. All subjects actively complied with the treatments, and there was a low number of dropouts (some teeth were restored and two patients did not come to the last visit). In contrast to previous studies, no negative control group or placebo was included because of ethical concerns. Since our study was longer than one month, the Ethical Committee did not approve the inclusion of a negative control (no treatment).

Table 1: *Means and Standard Deviations of the Baseline to Final Visual Analog Scale Scores Presented by the Teeth Treated With the Different Desensitizing Materials for the Comparison Among the Treatments in Each Time of Analysis*[a]

Period	Materials			
	Desensibilize Nano-P	**Desensibilize Nano-P and Experimental Home Care**	**Pro-Relief Professional and Home Care**	**Duraphat-NaF varnish (D)**
first month	4.10 ± 3.50 (n= 31)	4.48 ± 2.57 (n= 22)	3.82 ± 2.75 (n= 28)	3.35 ± 2.63 (n= 50)
third month	4.52 ± 2.86 (n= 30)	4.73 ± 2.22 (n= 22)	5.21 ± 2.27 (n= 26)	2.61 ± 2.16 (n=45)

[a] *n= number of teeth available at the moment of each period of analysis. There were no differences among the treatments for both periods (p>0.05).*

Table 2: *Means and Standard Deviations of the Baseline to Final Visual Analog Scale Scores Presented by the Different Treatments for the Comparison Between One Month and Three Months*[a]

Period	Materials			
	Desensibilize Nano-P (n= 30)	Desensibilize Nano-P and experimental home-care (NpPH) (n= 22)	Pro-Relief professional and home-care (PR) (n= 26)	Duraphat-NaF varnish (D) (n= 44)
first month	4.08 ± 3.56a	4.48 ± 2.57a	4.13 ± 2.60a	2.81 ± 2.21a
third month	4.52 ± 2.86a	4.73 ± 2.22a	5.21 ± 2.27b	2.53 ± 2.13a

[a] *n= the number of teeth included only when they were evaluated at both period. One tooth from the Duraphat group (n = 44 instead of 45) was excluded due to the lack of data at the first month. Treatments whose means are followed by distinct letters in the same column differ significantly (p=0.049).*

It is also important to highlight that DH is a subjective condition that is difficult to quantify. Evaporative stimuli and the VAS scale, applied in the present study, are acceptable methods to provoke and quantify the pain, respectively.[29,30] The evaporative method has been shown to be more precise than the tactile method to provoke DH.[31] Similar initial conditions were ensured by the randomized distribution of the patients with similar baseline VAS among the treatments.

The mechanism of action of most desensitizing treatments is based on obliteration of the dentin tubules by salt precipitation, avoiding movement of the fluid and stimulus of the nervous processes.[10,32,33] The longevity of the precipitates on or inside the dentin tubules and their ability to resist acid and mechanical challenges over time are still under discussion. Accordingly, in the present study we did not evaluate the immediate effect of the treatments but their effect after one month and three months of the last professional application.

The NaF varnish was included in the present study as this product is widely applied in the professional treatment of DH.[9,12-16,33] However, long-lasting efficacy of the NaF varnish treatment has been previously discussed.[34] Corroborating our results, Yilmaz and others[15] pointed out that NaF varnish has an immediate relief effect that is lost after three months of application. Kielbassa and others[16] showed a great hypersensitivity relief after three weeks of treatment with NaF/CaF_2 lacquer, and this effect was stable for 12 months. Our VAS values are very close to what Kielbassa and others[16] found; however, in the previous study NaF products were not compared with any other treatment. In our study, NaF varnish presented a low clinically relevant effect against DH compared with the other treatments after three months (not significant).[13] Therefore, we can infer that the CaF_2 precipitates produced by NaF varnish application are not resistant to the oral environment, and fluoride can be released to saliva over time.[15,33,35,36]

Recently, Pro-Argin (8.0% arginine) in-office and home-care desensitizing pastes have become popular for the DH treatment. Most studies are focused on the effect of Pro-Argin toothpaste (home-care application) compared with conventional or antisensitive toothpastes in the treatment of DH.[19,37,38] Pro-Argin toothpaste was able to relieve hypersensitivity compared with a conventional toothpaste for two, four, and eight weeks.[37] With respect to the professional application, Kapferer and others[18] showed that Pro-Argin in-office paste provided higher hypersensitivity relief compared with negative control (immediate and at four and 12 weeks). In the present study, Pro Relief (professional and home care) was the unique treatment that showed progressive effect on the reduction of DH over time, in agreement with previous studies.[17,36,37] However, the three-month analysis did not reveal any difference in the comparison among all the tested treatments. This positive finding might be attributed to the association between professional and home-care products, which likely allowed this relevant clinical effect. Furthermore, to the best of our knowledge, no studies have associated both professional and home-care Pro-Argin pastes. The longevity (>three months) of the plugs containing arginine, calcium carbonate, and phosphate inside the tubules[20] should be tested in the future using methods as scanning electron microscopy and hydraulic conductivity tests. It would be also very interesting to compare the effect of the in-office treatment, with and without the inclusion of the home-care toothpaste, to better understand the contribution of both products to DH control. A recent systematic review highlighted the lack of confident randomized clinical trials to give evidence on the use of arginine-based products over time.[39]

On the other hand, nano-HA paste technology has been recently developed in dentistry, especially for the remineralization of carious lesions.[21,24-26] With respect to DH, only one study, by Shetty and others,[27] showed that HA has potential as an effective and permanent desensitizer when used as

an in-office treatment compared with no treatment or distillated water after one day and one, two, four, and eight weeks. The authors discussed the need for comparative clinical trials with other popular desensitizing methods.

In the current study we tested Desensibilize Nano-P professional and home-care pastes as an innovative treatment for DH and compared the effectiveness of professional paste application, with or without the home-care paste, in reducing DH. It is important to highlight that the Nano-P paste contains no abrasives or detergents. Therefore, it is not considered a toothpaste to be applied during toothbrushing but a complementary method to be used after toothbrushing.

Both Desensibilize Nano-P and experimental home-care nano pastes were as effective in reducing DH as the Pro-Argin technology after one and three months. However, we found an interesting result for Desensibilize Nano-P—the professional paste was able to reduce DH regardless of the inclusion of home-care treatment. This is an important contribution of this study; three applications of Desensibilize Nano-P were enough to achieve good control of DH for three months, with no need of further visits and patient compliance for home-care application, in agreement with Shetty and others.[27]

Based on this, we can speculate that the professional paste might provide a mechanical imbrication of the nano-sized HA into or onto the dentin tubules, which was resistant to the oral environment for three months. We should also consider a possible role of fluoride and potassium nitrate as active agents included in the Desensibilize Nano-P and experimental nano home-care pastes. It has been discussed that potassium salts are able to inactivate intradental nerves. However, this principle has never been confirmed. The mechanism of the desensitizing effects of potassium-containing toothpastes remains uncertain.[9]

In the future, the longevity of the treatment with nano-HA should be tested, by extending the evaluation time, to determine when the professional paste should be reapplied. Furthermore, studies focusing on the mechanism of action are necessary to evaluate the dentin morphologic changes and the permeability alterations after the Desensibilize Nano-P application.

It should be highlighted that the positive results of the present study might be also partially attributed to reparative dentin (secondary and tertiary dentin), the natural course of the condition over the three months (especially in case of intolerable baseline pain, which can not be worse overtime), and positive changes in patient behavior during the study (Hawthorne effect). However, these effects are likely to happen for all treatments and would not interfere in their comparison.

CONCLUSION

Considering the experimental design and the findings, this randomized clinical trial demonstrated that Desensibilize Nano-P (with or without home-care product association) was as effective as the other treatments for reducing DH over three months.

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Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of Bauru School of Dentistry. The approval code for this study is 160/2010.

Conflict of Interest

The authors of this manuscript certify that they have no proprietary, financial, or other personal interest of any kind in any product, service, and/or company that is presented in this article.

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